

【 Document Name 】 APPLICATION FOR PATENT
【 Reference Number by Applicant 】 D-11406
【 Submitting Date 】 April 23, 1993
【 Addressee 】 Commissioner of Patent Office
【 IPC 】 C07C 229/42
【 Title of Invention 】
External Anti-inflammatory and Analgesic Plaster Preparation
【 Name of Claims 】 4
【 Inventor 】
 【 Address 】 1472-2, Higashiyama, Shirotori-cho,
 Okawa-gun, Kagawa, Japan
 【 Name 】 Mitsuji AKAZAWA
【 Applicant 】
 【 Address 】 567, Sanbonmatsu, Ouchi-cho,
 Okawa-gun, Kagawa, Japan
 【 Name 】 TEIKOKU SEIYAKU CO., LTD
 【 Representative 】 Shozo AKAZAWA
【 Applicant 】
 【 Address 】 Via Dogana Vicchia 2, CH-6900,
 Lugano, Switzerland
 【 Name 】 ALTERGON S.A.
 【 Nationality 】 Switzerland
【 Attorney 】
 【 Identification Number 】 100065385
 【 Patent Attorney 】
 【 Name 】 Johei YAMASHITA
 【 Telephone 】 03-3431-1831
【 Indication of Fee 】
 【 Method of Payment 】 Prepayment
 【 Number of Account 】 010700
 【 Amount of Payment 】 14000
【 List of Attached Objects 】

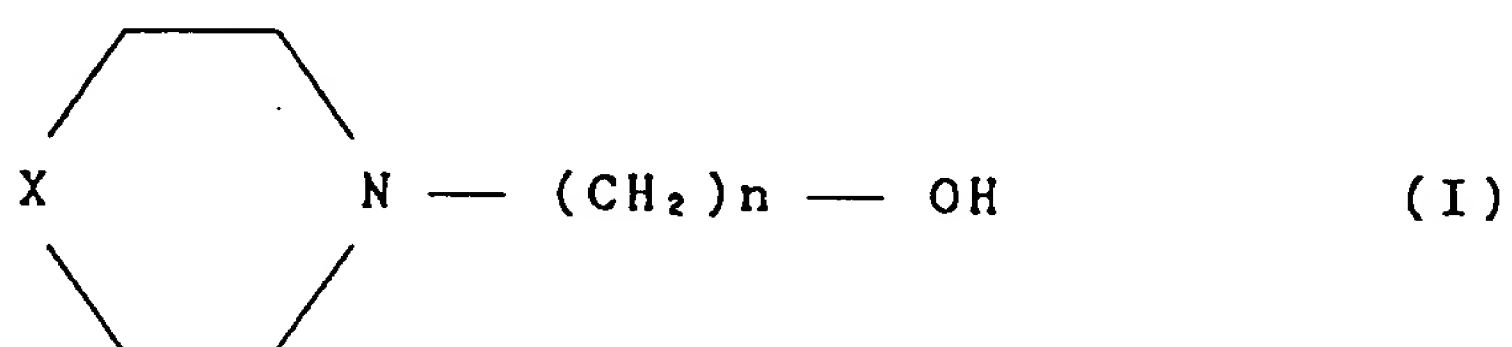
【 Name of Object】	Specification	1
【 Name of Object】	Drawing	1
【 Name of Object】	Abstract	1

[Name of the Document] Specification

[Title of the Invention] External Anti-inflammatory and Analgesic Plaster Preparation

[Claimed Scope of the Invention]

[Claim 1] An external anti-inflammatory and analgesic plaster preparation characterized in that the said preparation contains a salt of diclofenac, 2[(2,6-dichlorophenyl)amino]benzene-acetic acid with a cyclic organic base having the general formula (I)

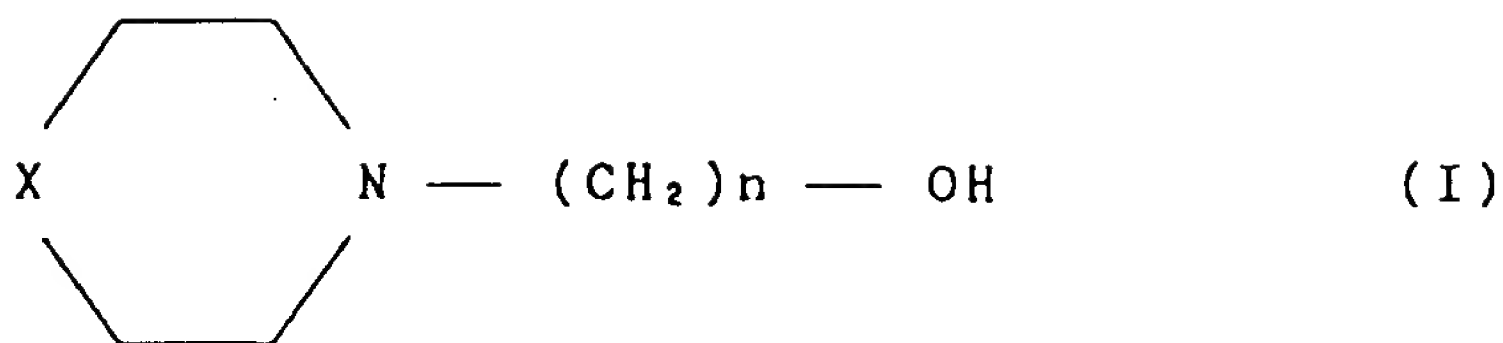


wherein X is a group of the formula $-(\text{CH}_2)_m-$ in which m is an integer of 0 or 1 and n is an integer of 2 as an active ingredient, a pH adjuster and optionally, a pharmaceutically acceptable ingredient such as thickening agents, humectants, fillers, preservatives and cross-linking agent and also, a pH value of the said preparation is adjusted to a range of 7.3 to 9.0.

[Claim 2] The external plaster preparation of claim 1 wherein the cyclic organic base of general formula (I) is hydroxyethyl-pyrrolidine or hydroxyethylpiperidine.

[Claim 3] The external plaster preparation of claim 1 wherein the pH value of the said preparation is within a range of 7.5 to 8.5.

[Claim 4] A process for producing an external anti-inflammatory and analgesic plaster preparation, characterized by subjecting a composition comprising a salt of the above-mentioned diclofenac with a cyclic organic base of general formula (I),



wherein X and n are as defined above as an active ingredient, a pH adjuster and optionally, as a pharmaceutically acceptable ingredient, such as thickening agents, humectants, fillers, preservatives and cross-linking agents to steps of incorporating each ingredient, dissolving or dispersing a part or all of the ingredients in water and kneading one ingredient with other ingredients while adjusting and maintaining a pH of the composition at a range of 7.3 to 9.0 during the step of preparation and then, spreading the resulting product over a support.

[Detailed Description of the Invention]

[0001]

[Filed of Application in Industry]

This invention relates to an external anti-inflammatory and analgesic agent. More particularly, it is concerned with an external anti-inflammatory and analgesic plaster preparation wherein a salt of diclofenac with a cyclic organic base is contained as an active ingredient and release and absorption are remarkably improved.

[0002]

[Prior Art]

Where various non-steroidal anti-inflammatory and analgesic agents are orally administered, an efficient drug distribution in inflammatory sites is difficult to be achieved and further undesirable side-effects could be produced in gastrointestinal tracts in such diseases developed relatively locally near body surface as arthritis, sarcitis, tenovaginitis and the like.

[0003]

Accordingly, there have been developed in the field of orthopedics ointments containing various non-steroidal agents in order to avoid systemic side-effects and they have been medicinally supplied as a practical pharmaceutical preparation. Also, there have been proposed plaster preparations as another pharmaceutical preparation having the same efficacy. The plaster preparation could have many advantages not seen in the ointments, such as prolonged effects, precise dosages, simple administration, cooling effects on diseased parts by the free water involved in the base and fixing effects on diseased parts by the preparation. Presently, there have been supplied those plaster preparations containing three sorts of non-steroidal agents, indomethacin, Ketoprofen and flurbiprofen and their usefulness has been appraised. However, these agents have an extremely low solubility in water and thus it is essential to add a specific drug solubilizer or solubilizing agent.

[0004]

On the other hand, Japanese Patent Kokai Koho No. 63-152372 discloses a salt of diclofenac with an organic cyclic base and a pharmaceutical composition containing same, in which it is reported that the pharmaceutical compositions containing the diclofenac salt are effective as an anti-inflammatory and analgesic for oral administration.

[0005]

Hitherto, there have been used external anti-inflammatory and analgesic plaster preparations of a diclofenac type containing diclofenac-Na salt as an active ingredient. Since the diclofenac-Na salt has a low solubility to water so that a skin permeability is reduced and therefore, a sufficient pharmacological effect can not be obtained when applied to the skin.

[0006]

For overcoming such disadvantages, there have been provided various improvements in the external diclofenac-containing plaster preparations. As disclosed in, for example, Japanese Patent Kokai Koho Nos. 57-24308, 57-81409, 60-208909, 61-60608 and 62-181226, there are provided the external anti-inflammatory and analgesic plaster preparations having added a dissolution assistant to raise the solubility of diclofenac Na-salt or having an absorption accelerator to raise the permeability to skin.

[0007]

[Problems to be solved by the Invention]

However, there are problems that the addition of the dissolution assistant or absorption accelerator results in loss of freedom in a design for preparation and also, the skin subjected to treatment is injured by the dissolution assistant or absorption accelerator used.

[0008]

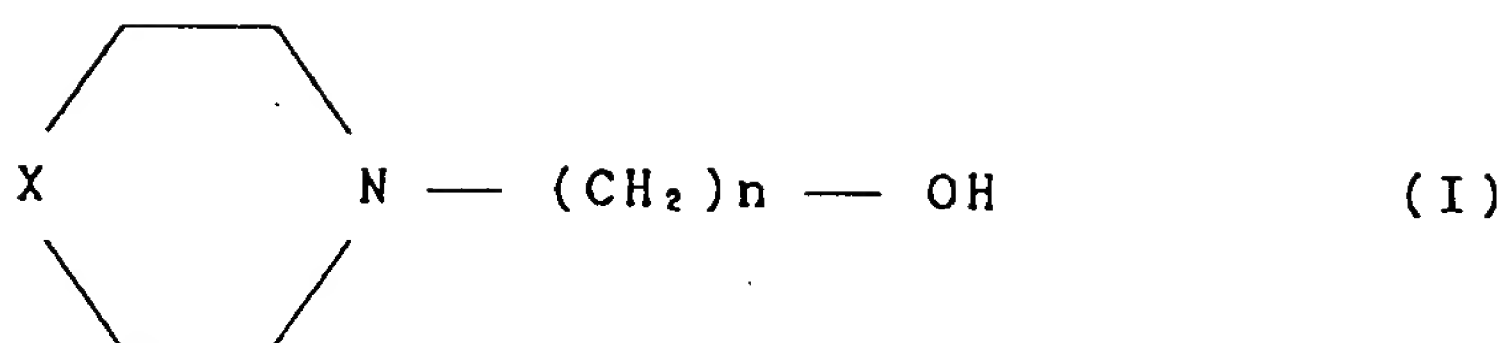
Accordingly, an object of the present invention is to provide an anti-inflammatory and analgesic plaster preparation having a sufficient pharmacological effect with good absorption to skin and prolonged effects in respect of the diclofenac-containing anti-inflammatory and analgesic plasters which were regarded as difficult for preparation.

[0009]

[Means for dissolving the Problems]

In accordance with the present invention, there is provided an external anti-inflammatory and analgesic plaster preparation characterized in that the said preparation contains as an active ingredient a salt of diclofenac 2[(2, 6-dichlorophenyl) amino]benzene-acetic acid, with a cyclic organic base having the general formula (I)

[0010]



wherein X is a group of the formula $-(\text{CH}_2)_m-$ in which m is an integer of 0 or 1 and n is an integer of 2) and a pH value of the said preparation is adjusted to a range of 7.3 ~9.0.

[0011]

Also, the plaster preparations of the present invention are obtained by a process characterized by subjecting a composition comprising the above salt of diclofenac with the cyclic organic base of the above general formula (I) as the active ingredient, a pH adjuster and optionally, a pharmaceutically acceptable ingredients such as thickening agents, humectants, fillers, preservatives and cross-linking agents to steps of incorporating ingredients, dissolving or dispersing a part or all of the ingredients in water and kneading one ingredient with other ingredients while adjusting and maintaining a pH of the composition at a range of 7.3 to 9.0 during the steps of preparation and then, spreading the resultant product over a support.

[0012]

An amount of the salt of diclofenac with a cyclic organic base, as the active ingredient, to be incorporated in the present plaster preparation may be of a sufficient amount to accomplish the desired therapeutic effect and is not generally critical. Usually, the amount is recommended to be 0.1~5.0% by weight, preferably 0.3~3.0% by weight. As the cyclic organic base, there may be mentioned, for example, hydroxyethylpyrrolidine, hydroxyethylpiperidine and the like.

[0013]

It is recommended that a composition for the present

plaster preparation may have a pH value of 7.3 ~9, preferably 7.5~8.5. At a pH value of less than 7.3, water-in soluble diclofenac crystals may be separated out, while, when a pH value is higher than 9, it may be feared to induce skin irritation. For adjusting a pH value of the composition, there may be used any organic or inorganic acid or base and there is no particular limitation thereto. And, its amount to be employed may vary upon the pH value of the composition and, the sort of a pH adjuster and there is no particular limitation thereto.

[0014]

Other optional components which may form the present plaster preparation may be thickening agents, humectants, fillers, preservatives, cross-linking agents and others commonly employed in a pharmaceutical field. For instance, one may use as thickening agents polyacrylic acid, sodium polyacrylate, carboxymethylcellulose sodium (CMC Na), polyvinyl alcohol, polyvinyl pyrrolidone, gelatin and others; a preferable amount of these components 3-30% by weight, more preferably 5-20% by weight. When used in amount less than 3% by weight, the preparation penetrates through the base fabric or leaves on the skin due to its less viscosity. As humectants, glycerol, propylene glycol, polyethylene glycol, 1,3-butanediol, D-sorbitol solution and other can be used. A preferable amount of these components 5-70% by weight, more preferably 10-60% by weight. When used in amount less than 5% by weight, the humectant effect could be not sufficient and dries rapidly upon being stuck. More than 70% will cause it difficult to blend other components. As fillers, kaolin, bentonite and others; as preservatives, paraoxybenzoic acid esters, sorbic acid and others. As cross-linking agents, aluminum compounds, calcium compounds and others. Recommended amount is 0.01-3.0% by weight. When used in amount less than

0.01% by weight, the heat resistance property becomes not sufficient due to less cross-linking rate, and tends to leave on the skin or flow into the package. More than 3.0% will lower the productivity on kneading and spreading due to higher viscosity, and also lower the sticking force of the preparation. They may be employed to afford shape retention and water retention as required for a plaster preparation.

[0015]

The present plaster preparation are obtained by dissolving or dispersing a part of the components in water and kneading together. In this connection it is necessary to adjust a pH of the composition not less than 7.3 at the time when the drugs are added and to adjust and maintain the pH of the composition not less than 7.3 from the beginning to the end of preparation, because diclofenac may be separated out as crystals at a pH value less than 7.3 and the crystals once separated could not be readily dissolved even if the pH value may be then increased to exceed 7.3.

[0016]

There is no restriction on the order of addition of pH adjusting agent in the production process.

[0017]

For example, when an acidic thickening agents is used, the medicines are added after the pH is adjusted to 7.3-9.0 by a pH adjusting agent. There is no limitation on the order of addition of the thickening agent and pH adjusting agent. While, when an alkaline thickening agents is used, the pH is adjusted to 7.3-9.0 by a pH adjusting agent after the medicines are added. After the medicines are added, there is no problem in adding any component which does not lower the pH less than 7.3.

[0018]

The present plaster preparation may be finally prepared

by blending the salt of diclofenac with a cyclic organic base with the above components, kneading together and spreading the resultant product over a support. There is no particular limitation to spreading methods and a thickness of the preparation, but a therapeutic effect in sealed form may be expected by designing a thickness of the preparation as relatively thicker (e.g., not less than 0.5mm), together with the effect by the support.

[0019]

As the support, there is no particular limitation, but there may be desirably employed any flexible materials such as fabrics, non-fabrics, papers, plastic films and laminates thereof, which may easily follow the movement of a person applied.

[0020]

In the present plaster preparation thus prepared, the active ingredient, the salt of diclofenac with the cyclic organic base, is being stably dissolved in the preparation without separation as crystals by adjusting a pH value of the base to 7.3-9, whereby the release and absorption of drug are remarkably improved, the utility rate of the drug is extremely high and superior effects are obtained.

[0021]

[Examples]

This invention will be more fully described by way of the following examples, but this invention is not to be limited to these examples.

[0022]

[Example 1]

[Components]	[% (w/w)]
Diclofenac hydroxyethylpyrrolidine (DHEP)	1.3
Sodium polyacrylate	4
CMC Na	3

Gelatin	2
Polyvinyl pyrrolidone	2
1,3-Butanediol	20
D-sorbitol solution	20
Kaolin	5
Titanium oxide	0.5
Aluminum hydroxide	0.8
Tartaric acid	0.3
Methylparaben	0.1
Propylparaben	0.05
Purified water	q.s.

Total	100
-------	-----

[0023]

To 30 parts of the purified water were added the gelatin and polyvinyl pyrrolidone and they were dissolved by heating at 60°C. To the resulting solution were added the D-sorbitol solution, Kaolin, titanium oxide, methylparaben and propylparaben and a sufficient kneading was carried out. Then, a solution of the sodium polyacrylate, CMC Na and aluminum hydroxide dispersed in the 1,3-butanediol was further added and then a further kneading was carried out. Finally, the DHEP dissolved in the remainder of the purified water was added and the resulting mixture was further kneaded until it became homogeneous. The plaster thus obtained was spread over a non-woven fabric at 100g/m². The fabric was stuck on a plastic film and cut into a desired size to prepare a plaster preparation. The preparation as formed had a pH value of 7.9.

[0024]

[Example 2]

[Components]

	[%(w/w)]
DHEP	1.3
Sodium polyacrylate	2

Polyacrylic acid	2
CMC Na	3
Gelatin	2
Polyvinyl alcohol	1
Glycerol	30
Kaolin	10
Aluminum hydroxide	0.8
Triethanolamine	1.5
1N-Sodium hydroxide	0.3
Methylparaben	0.1
Propylparaben	0.05
Purified water	q.s.

Total	100
-------	-----

[0025]

To 30 parts of the purified water were added the gelatin and polyvinyl alcohol and they were dissolved by heating at 60°C. To the resulting solution were added the polyacrylic acid, D-sorbitol solution, Kaolin, methylparaben, propylparaben and 1N-sodium hydroxide and a sufficient kneading was carried out. Then, a solution of the sodium polyacrylate, CMC Na, triethanolamine and aluminum hydroxide dispersed in the glycerol was further added and then a further kneading was carried out. Finally, the DHEP dissolved in the remainder of the purified water was added and the resulting mixture was further kneaded until it became homogeneous. The plaster thus obtained was spread over a non-woven fabric at 800g/m². The fabric was stuck on a plastic film and cut into a desired size to prepare a plaster preparation. The preparation as formed had a pH value of 7.8.

[0026]

[Example 3]

[Components]

[%(w/w)]

DHEP	0.65
Sodium polyacrylate	4
CMC Na	2.5
Gelatin	2
Polyvinyl alcohol	3
Propyleneglycol	10
D-sorbitol solution	30
Kaolin	5
Aluminum acetate	1.2
Propylparaben	0.1
Purified water	q.s.

Total	100
-------	-----

[0027]

To 30 parts of the purified water were added the gelatin and polyvinyl alcohol and they were dissolved by heating at 60°C. To the resulting solution were added the D-sorbitol solution, Kaolin and propylparaben and a sufficient kneading was carried out. Then, the DHEP dissolved in the remainder of the purified water was added and a further kneading was carried out. Finally, a solution of the sodium polyacrylate CMC Na and aluminum acetate dispersed in the propylene glycol and the resulting mixture was further kneaded until it became homogeneous. The plaster thus obtained was spread over a non-woven fabric at 1000g/m². The fabric was stuck on a plastic film and cut into a desired size to prepare a plaster preparation. The preparation as formed had a pH value of 8.5.

[0028]

[Comparative Example 1]

[Components]	[% (w/w)]
Diclofenac Na	1
Sodium polyacrylate	4
CMC Na	3

Gelatin	2
Polyvinyl pyrrolidone	2
1,3-Butanediol	20
D-sorbitol solution	20
Kaolin	5
Titanium oxide	0.5
Aluminum hydroxide	0.8
Tartaric acid	0.3
Methylparaben	0.1
Propylparaben	0.05
Purified water	q.s.

Total	100
-------	-----

[0029]

Following the same procedure as described in Example 1 except that diclofenac Na was employed instead of the DHEP, there was formed an external plaster preparation. The preparation as formed had a pH value of 8.0.

[0030]

[Comparative Example 2]

[Components]	[% (w/w)]
DHEP	1.3
Sodium polyacrylate	2
Polyacrylic acid	2
CMC Na	3
Gelatin	2
Polyvinyl alcohol	1
Glycerol	30
Kaolin	10
Aluminum hydroxide	0.4
Tartaric acid	0.3
Methylparaben	0.1
Propylparaben	0.05

Purified water	q.s.

Total	100
-------	-----

[0031]

To 30 parts of the purified water were added the gelatin and polyvinyl alcohol and they were dissolved by heating at 60°C. To the resulting solution were added the polyacrylic acid, D-sorbitol solution, Kaolin, methylparaben, propylparaben and tartaric acid and a sufficient kneading was carried out. Then, a solution of the sodium polyacrylate, CMC Na and aluminum hydroxide dispersed in the glycerol was added and a further kneading was carried out. Finally, the DHEP dissolved in the remainder of the purified water was added and a further kneading was carried out until it became homogeneous. The plaster thus obtained was spread over a non-woven fabric at 1000g/m². The fabric was stuck on a plastic film and cut into a desired size to prepare a plaster preparation. The preparation as formed had a pH value of 6.8.

[0032]

[Test Example 1]

The skin excised from the rat abdomen was placed into Franz diffusion cell, while each of the test preparation obtained by Examples 1 and 2 and Comparative Example 1 and was punched into a circle with a diameter of 1.7cm, which was then put on the rat skin (n=7). An amount of the drug permeated through the rat skin after a given time was determined by HPLC using a phosphate buffer at pH 7.0 on a receptor side. The results are shown in FIGURE 1.

[0033]

As apparent from FIGURE 1, the present plaster preparation showed a far better skin permeability as compared with the plaster preparation of diclofenac Na incorporated into the same composition. Also, the plaster preparation

(Comparative Example 2) having a pH value of 6.8, thought it contained the same drug as used in the present plaster preparation, apparently showed an inferior skin permeability to that of the present plaster preparation.

[0034]

[Test Example 2]

For evaluation of an analgesic effect of the plaster preparation, a carrageenin edema rate was measured as follows:

[0035]

Wistar rats weighing 150~180g were used, a group consisting of 10 animals. A volume of right hind leg of each rat was measured prior to the administration of the drug. Thereafter, each of the plaster preparations obtained by Examples 1 and 3 and Comparative Example 1 was cut to a sheet with 3×4 and then applied. After 4 hours from the administration, the plaster preparation was peeled off and immediately 0.1 of a 1 w/v% suspension of carrageenin was injected subcutaneously into the plantar of rat. Volumes of leg were measured at 2, 3 and 4 hours after the injection and an edema rate was calculated from the leg volume prior to the carrageenin injection according to the following equation:

[0036]

$$\text{Edema rate (\%)} = \frac{V - V_0}{V_0} \times 100$$

where

V_0 : Leg volume prior to the carrageenin injection.

V : Leg volume at every measuring time after the carrageenin injection.

The results are shown in FIGURE 2.

[0037]

As apparent from FIGURE 2, the present plaster preparation showed a higher edema-inhibitory effect as compared with the conventional plaster preparation containing

a diclofenac derivative.

[0038]

Test Example 3

In order to determine whether or not there may be found any crystals of diclofenac in plaster preparations, a polarizing microscopic observation was carried out on the test preparations immediately after prepared in Examples 1, 2 and 3 and Comparative Example 2 and after storage for 24 hours at 5°C and room temperature.

The results are shown in Table 1.

[0039]

	TABLE 1		
	IMMEDIATELY AFTER PREP. -----	5°C, 24Hrs. -----	Room Temp. 24Hrs. -----
Example 1	not observed at all	not observed at all	not observed at all
Example 2	not observed at all	not observed at all	not observed at all
Example 3	not observed at all	not observed at all	not observed at all
Comparative Example 2	slightly observed	many observed	many observed

[0040]

[Effect of the Invention]

As apparent from the Table 1, any separation of crystals was not observed at all in the present plaster preparation. However, separation of many crystals was observed after one day in the preparation obtained by Comparative Example 2 having a lower pH value.

[Breif Description of the Drawings]

[Fig. 1]

FIGURE 1 shows a relationship between the sticking time onto the rat skin and the amount of the drug permeated.

[Fig. 2]

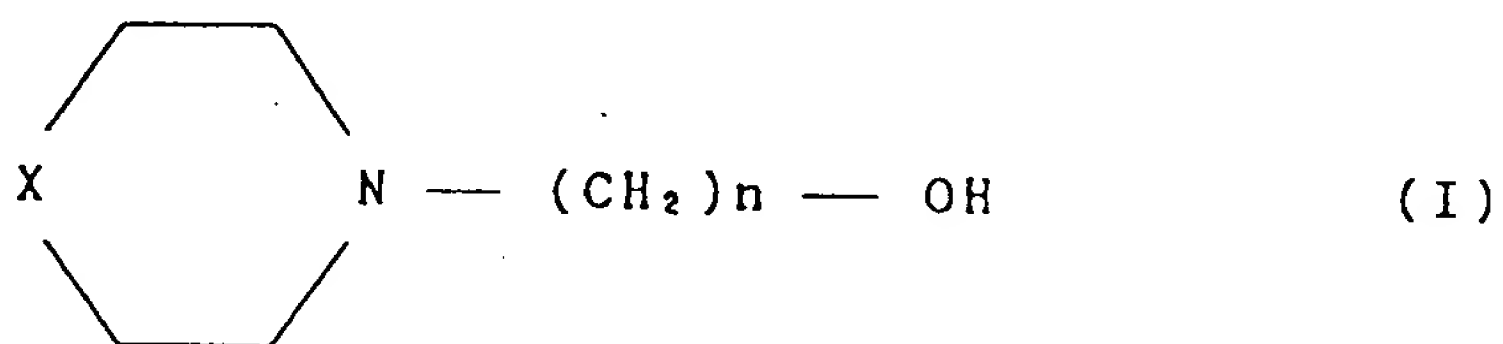
FIGURE 2 shows a relationship between the times lapsed after carrageenin injection and the edema rate (%) of the rat plantar.

[Name of the Document] Abstract

[Abstract]

[Object]

[Construction] An external anti-inflammatory and analgesic plaster preparation includes as an active ingredient a salt of diclofenac, 2[(2,6-dichlorophenyl)amino]benzene-acetic acid, with a cyclic organic having the general formula (I):



wherein X is a group of the formula $-(\text{CH}_2)_m-$ in which m is an integer of 0 or 1 and n is an integer of 2 and a pH value of the preparation is adjusted to a range of 7.3~9.0.

FIG. 1

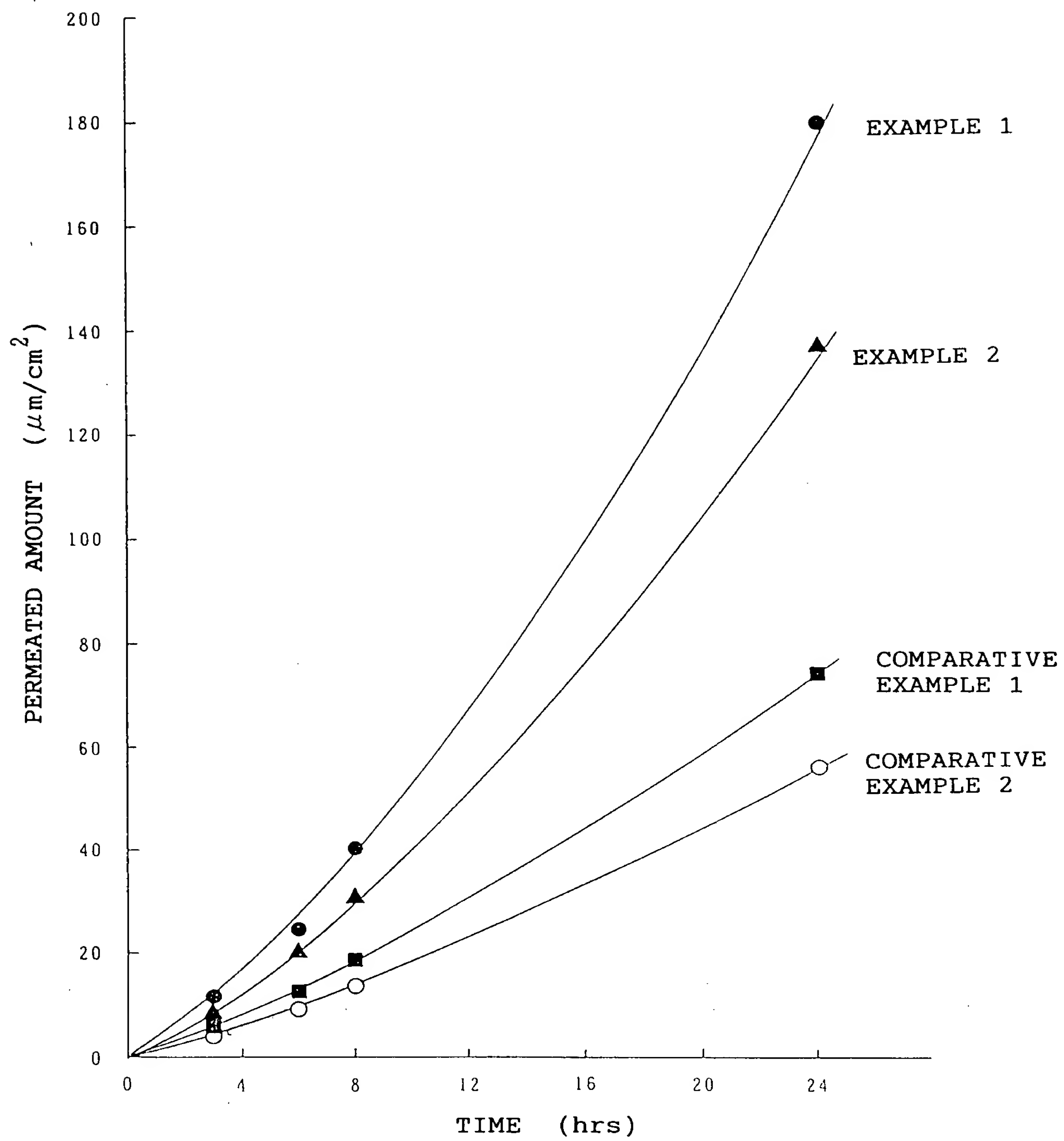
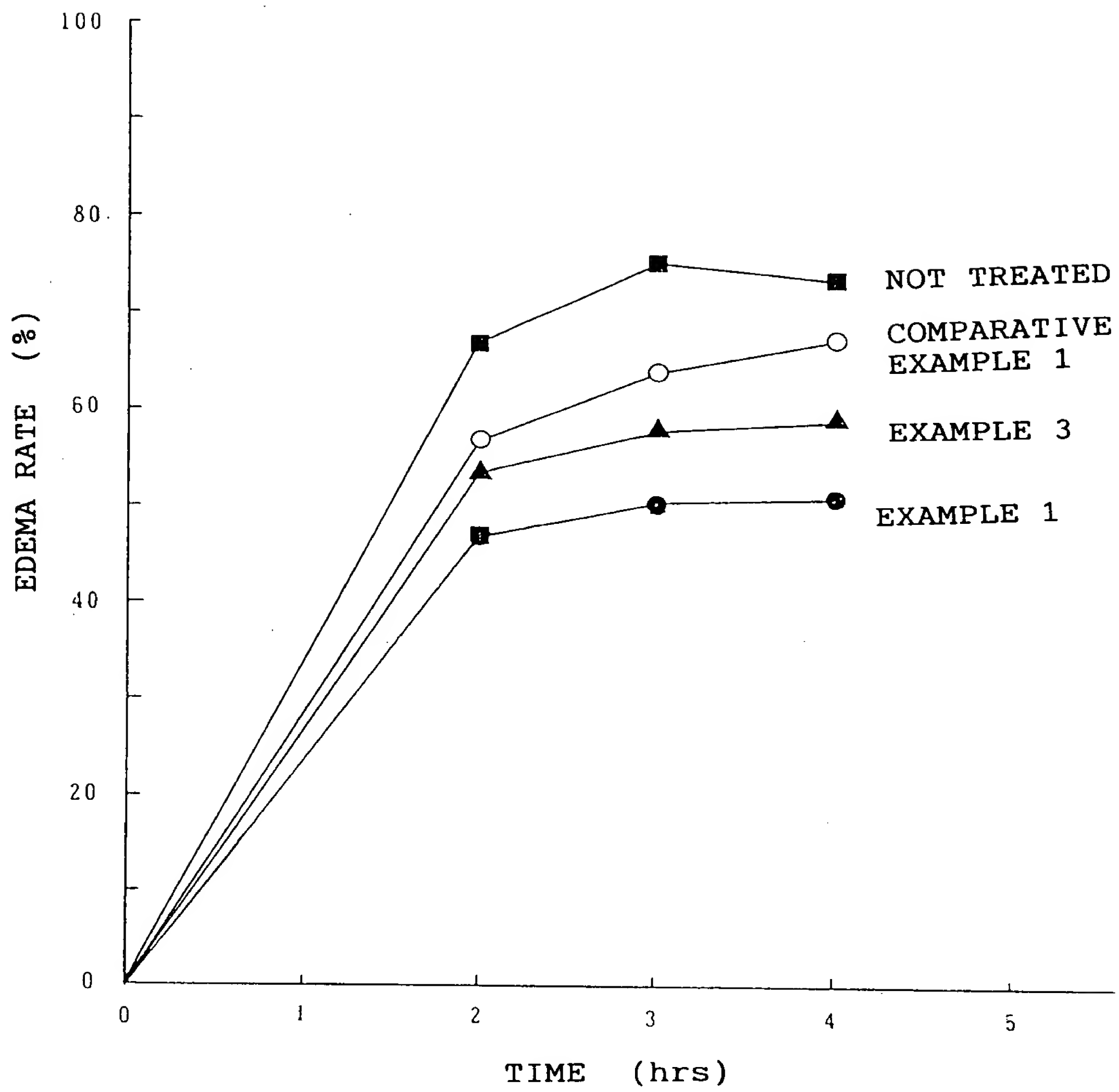


FIG. 2





UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: Box ISSUE FEE
COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

15M1/0909

LAWRENCE A STEWARD
BAKER & DANIELS
300 NORTH MERIDIAN STREET
SUITE 2700
INDIANAPOLIS IN 46204

**NOTICE OF ALLOWANCE
AND ISSUE FEE DUE**

☐ Note attached communication from the Examiner

☐ This notice is issued in view of applicant's communication filed _____

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/579,469	12/27/95	004	PHILAN, D	1502 09/09/96
First Named Applicant	AKAZAWA, MITSUJI			

TITLE OF INVENTION
EXTERNAL ANTI-INFLAMMATORY AND ANALGESIC PLASTER PREPARATION

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1	424-443.000	E01	UTILITY	NO	\$1250.00	12/09/96

**THE APPLICATION IDENTIFIES ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT.
PROSECUTION ON THE MERITS IS CLOSED.**

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

- I. Review the SMALL ENTITY Status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
 - A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the patent and Trademark Office of the change in status, or
 - B. If the Status is the same, pay the FEE DUE shown above.
- II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.
- III. All communications regarding this application must give series code (or filing date), serial number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to contrary.

If the SMALL ENTITY is shown as NO:
A. Pay FEE DUE shown above, or
B. File verified statement of Small Entity Status before, or with, pay of 1/2 the FEE DUE shown above.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.